Assessment of Tumor Blood Flow Using Positron Emission Tomography and H2150: Effect of Hydralazine

IV. 4. Assessment of Tumor Blood Flow Using Positron Emission Tomography and $H_2{}^{15}O$: Effect of Hydralazine

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Introduction

The role of antihypertensive agents, such as hydralazine, on reducing tumor blood flow is, recently, emphasized, which subsequently increases the hypoxic fractions in the tumor. Such increased hypoxic cells are aimed by anti-tumor agents which selectly kill hypoxic fractions of the tumor.[1] For this purpose, it is necessary to study not only how to reduce the tumor blood flow but how to measure the tumor blood flow and how to watch the change of the blood flow following administration of such antihypertensive agents.

We are studying experimentally how to measure and watch the change of the tumor blood flow using a positron emission tomography (PET) and $H_2{}^{15}O$. We think this method is convenient and feasible for human use. We have constructed and tested the system using rabbit tumor model and antihypertensive agents.

Materials and Methods

Tumor (VX2) was implanted into the left thigh of the rabbits. Tumor grew up to, at least, 4 - 6 cm in diameter, the experiment was performed. They were anesthetized by intravenous administration of sodium pentobarbital (50 - 100 mg/kg) and were catheterized through right common iliac artery. Blood pressure was monitored through this artery. Also arterial line to a beta detector was set and, at the end of this line, was connected to an infuse/withdrawal pump.

Hydralazine and nifedipine were chosen for antihypertensive agents. Hydralazine is a vasodilator and nifedipine is a calcium-channel blocker which cause vasodilatation. Hydralazine (0.4 mg/kg) was administered i.v. and nifedipine (5 mg/kg) was administered orally.

PET-931 (CTI) was used for scanner. After transmission scan, twenty times 6 seconds emission scans were performed immediately after bolus injection of $H_2{}^{15}O$ at the level of tumor. Arterial blood was also withdrawn by the pump and, simultaneously, the arterial blood beta-ray radioactivity was continuously recorded through the beta detector.

Two series of emission scans were performed; lst scan for control and 2nd scan for response to the antihypertensive agents. Region of interest (ROI) was set on the whole tumor image and contralateral normal tissues - muscles. Radioactivities of the ROI were listed as average and maximum counts. They were summed from 1 to 20 planes. Arterial blood counts were also integrated for 120 seconds as an arterial input. Comparison between the two scans was done as follows; summed ROI counts divided by the arterial input were compared and expressed as percentage blood flow change.

Results

Results are summarized in Table 1. After administration of nifedipine, mean blood pressure was down to 75 % and tumor and normal tissue blood flow were, also, down to 83 and 70 %, respectively.

After administration of hydralazine, mean blood pressure was down to 70 % for both studies. Average tumor blood flows were down to 91 % and maximal tumor blood flow were unchanged or, inversely, increased. Normal tissue blood flow was down to 70 % which was identical to the nifedipine study.

Discussion

There are lots of methods to measure the tumor blood flow. For clinical feasible study, we choose this method; PET and $H_2{}^{15}O$. There is another method for this purpose using PET; continuous inhalation of $C^{15}O_2$[2,3]. We did not adopt this method because inhalation of radioactive gas, causing accumulation of high radioactivity in the airway systems, such as nasal cavity, oral cavity, trachea and lungs, may hide tumors located in head, neck and lungs.

The advantages of our method are 1) repeated measurement of tumor blood flow, 2) comparison the results between the changes in tumor and that in normal tissues, 3) measurement of both absolute and relative changes of the tumor blood flow and 4) assessment of regional tumor blood flow.

Although nifedipine and hydralazine decreased blood pressure at the same extent, the effect of each agent on the tumor blood flow was different. The effect of hydralazine was not uniform. We think heterogenic response was found in the tumor vessels. In the tumor, there may be blood vessels which resist the vasodilating effect of hydralazine and this type of

tumor vessels belong to the fastest blood flow region. Heterogeneity of the blood flow in the tumor is well known[4]. We found heterogeneous response, so far, only to hydralazine in the tumor vessels. The precise mechanism is obscure. We are going to check this functional heterogeneity following administration of other vasoactive agents. We believe this is only our system that can detect functional heterogeneity in the tumor.

Quantitative assay of the tumor blood flow is undertaken right now. This project is not easy one. We needs help from all fields of the science: chemists, physists, computer engineers, physicians and so on. We are now constructing this system for routine use and will be accomplished very soon. We believe this system is worth while for cancer therapy.

References

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Table 1. Relative changes of tumor and normal tissue blood flow following administration of antihypertensive agents.

Exp.	Agent	% B.P.[a]	Region of Interest[b]		% Flow[c]
11-1	hydralazine[d]	72.2	tumor	(whole)	90.1
			tumor	(max)	101
			muscle	(whole)	69.1
			muscle	(max)	71.9
11-4	hydralazine	70.2	tumor	(whole)	92.6
			tumor	(max)	107
			tumor	(necrosis)	89.1
11-5	nifedipine[e]	74.5	tumor	(whole)	83.9
			tumor	(max)	82.2
			muscle	(whole)	72.2
			muscle	(max)	69.1

a) Relative change of mean blood pressure.
b) Max: Maximum count in the region of interest.
Whole: Average count in the region of interest.
Necrosis: Lower count region in the tumor.
c) Relative change of blood flow.
d) 0.8 mg i.v.
e) 1.0 ml p.o.